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## (54) SHORT-CHAIN TRIGLYCERIDES

KURZKETTIGE TRIGLYCERIDE

TRIGLYCERIDES A CHAINE COURTE

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- **Gastronterology 1988, vol.95, pp.715-720**
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## Descripti n

[0001] The present invention relates to parenteral nutrition and dietary supplements. More particularly, a new synthetic triglyceride family has been developed which provides numerous nutritional benefits and ease of breakdown when used either as a dietary supplement or fob total parenteral nutrition. This new structured lipid or synthetic triglyceride has at least one short-chain (2-5 carbon backbone) fatty acid attached to a glycerol backbone.

[0002] Structured lipids have recently become a fertile testing ground in the field of parenteral nutrition. Although the ability to form structured lipids through procedures such as transesterification has been known for many years, only recently has an understanding of how the particular fats work in the body when released from a triglycerol backbone been sufficiently developed so as to lead to further exploration of structured lipids for nutritional uses. For example, the nutritional advantages of ω3 fatty acids, primarily in the form of fish oil, are now well documented. In like manner, the advantages of medium chain triglycerides ($C_8$-$C_{12}$) for parenteral nutrition, particularly with hypercatabolic patients, are now being explored. (See, e.g., U.S. Patent No. 4,528,697.) However, not all structured lipids work alike, nor has it been possible to manufacture structured lipids with particular fatty acids on specific locations of the glycerol backbone until recently.

[0003] J. Dairy Sci. 47(7) (1964) pages 727-732 describes the triglyceride glyceryl 1-palmitate-2,3-dibutyrate.

[0004] Gastroenterology 95 (1988) pages 715-720 describes the use of short chain fatty acids in total parenteral nutrition in e.g. patients recovering from snail bowel resection. Am. J. Clin. Nutr. 36 (1982) pages 950-962 reviews the nutritional value of medium chain fatty acids.

[0005] Although medium-chain fatty acids and long-chain fatty acids have been tested for the nutritional benefits for a long time, only recently has any thought been given to benefits of short-chain fatty acids (2-5 carbon backbone). These short-chain fatty acids are made in the colon from complex carbohydrates and fibrous polysaccarides by bacterial fermentation. These complex carbohydrates, such as pectin and glucans, when broken down to the short-chain fatty acids by the colonic flora, are the preferred fuels for the large and small intestinal cells. e.g., the intestinal mucosa. It has been suggested that short-chain fatty acids could provide nutrition for critically ill patients who cannot obtain sufficient fiber in the diet. This is particularly important since lack of enteric feeding of critically ill patients can lead to translocation of bacteria and endotoxin from the intestinal lumen into vascular system because of thinned intestinal mucosa. This problem is not ameliorated by use of parenteral nutrition since the intestinal cells are ften deprived of their nec ssary nutrition.

[0006] However, the simple addition of short-chain fatty acids to parenteral nutrition does not appear to solve these problems. Short-chain fatty acids, when given as fatty acids, are potentially toxic. Moreover, since the short-chain fatty acids are much lower in calories than long-chain fatty acids, either a larger volume of the total parenteral nutrition diet must be used or the calorie content is decreased. Neither of these alternatives are good solutions for treating critically ill patients. In contrast, the synthetic triglyceride proposed herein can provide not only the short-chain fatty acids but also essential ω6 long-chain fatty acids as well as long-chain ω3 fatty acids.

[0007] Accordingly, an object of the invention is to provide a means of delivering short-chain fatty acids to the intestines as part of a total parenteral nutrition diet.

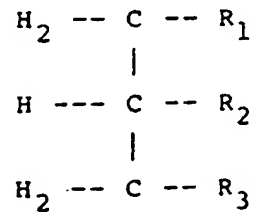
[0008] A further object of the invention is to provide a structured lipid containing short-chain fatty acids and medium or long-chain fatty acids.

[0009] Another object of the invention is to provide a structured lipid which, when fed enterally, enters the body through the portal system, partially bypassing the lymphatic system, while providing sufficient calories and delivery of the short-chain fatty acids to the intestinal mucosa.

[0010] These and other objects and features of the invention will be apparent from the following description and claims.

## Summary of the Invention

[0011] The present invention features a synthetic triglyceride of the form



where $R_1$, $R_2$ and $R_3$ meet the following criteria:

A. $R_1$, $R_2$ and $R_3$ are fatty acids with at least one, but not all of $R_1$, $R_2$ and $R_3$ being a short chain ($C_2$-$C_5$) fatty acid:

B. the fatty acids contain one short-chain fatty acid, are long-chain fatty acid and one medium-chain fatty acid;

C. $R_2$ is a medium-chain or short-chain fatty acid.

[0012] The invention also covers a total parenteral

nutrition diet for use in therapy, the diet having as its primary lipid source structured lipids in the form of triglycerides according to the invention.

**[0013]** The invention is useful in the treatment of those patients who have had small bowel resections, pancreatic or biliary insufficiency, or other maladsorption syndrome.

**[0014]** Most preferably, the preferred long chain fatty acid comprises an ω3 fatty acid having 18-22 carbon atoms in the carbon backbone, or an ω9 fatty acid.

**[0015]** As noted, the invention also finds application in the treatment of patients who have difficulty absorbing nutrients through the intestines by use of a total enteral or parenteral nutrition diet having structured lipids with short-chain fatty acids as at least one of the residues being the primary lipid source in the diet. Patients in this state include both critically ill patients and those who have had small bowel resections or other forms of maladsorption syndrome. All of the members of the family of structured lipids of the invention may be used to treat these patients.

**[0016]** The invention also finds application in the treatment of hypercatabolic patients by administering a parenteral diet having structured lipids with short-chain fatty acids as at least one of the residues as the primary lipid source. Again, the structured lipids of the invention are the preferred triglycerides for use according to the invention.

Description of the Invention

**[0017]** The present invention features a new family or class of structured lipids or synthetic triglycerides useful in treating critically ill or hypercatabolic patients. These structured lipids provide better feeding of intestinal cells in the intestinal mucosa than current parenteral nutrition diets while providing the benefits of medium-chain and or ω3 fatty acid additives.

**[0018]** The structured lipid of the invention may be formed by transesterification or any other lipid manufacturing process. Short-chain fatty acids useful in the invention include acetic acid, propionic acid, butyric acid, and valeric acid, preferably in the straight chain rather than branch chain forms. When used as part of a parenteral nutrition diet, the bonds holding the short-chain fatty acids to the glycerol backbone are broken in the body, particularly at the intestine. Therefore, the short-chain fatty acids are released at the proper location for use as energy sources for the intestinal mucosa. The addition of these structured lipids to a parenteral nutrition diet provides the substantial equivalent of the fibers common in most diets, e.g., pectin and glucans, which are broken down by the intestinal flora to these same short-chain fatty acids. These short-chain fatty acids traverse the intestinal mucosa, providing nourishment t the intestinal cells. Th us of this structured lipid ameliorates a problem common in conventional parenteral diets, that the body is able to function on the long-chain fatty acids used but the intestinal mucosa deteriorates because of lack of short-chain fatty acids. These synthetic triglycerides might even be helpful in the treatment, or prevention of colon cancer, providing some of the benefits of fiber in the diet.

**[0019]** Although the short-chain fatty acids may be located at any position on the triglycerol backbone, certain structured lipids within the broad family of the invention are preferred. If no other fatty calorie sources other than necessary amounts of linoleic acid are used in a total parenteral nutrition diet. synthetic triglycerides having ω3 fatty acids are preferred for use. The benefits of ω3 fatty acids in treatment of heart conditions, infection, and other conditions are well documented and new, positive applications of this family of fatty acids are being uncovered every day. Any long-chain fatty acids are in the $R_1$ or $R_3$ position on the triglycerides, leaving the $R_2$ position free for either short-chain fatty acid or medium-chain fatty acids. This $R_2$ position appears to have special properties, yielding the highest benefit if the proper residue for that position is selected judiciously.

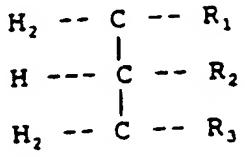
**[0020]** The structured lipids of the invention have medium-chain fatty acids on the triglyceride in addition to the short-chain fatty acids. Therefore, one achieves benefits for the hypercatabolic patients because of the medium-chain fatty acids while feeding and sustaining the intestinal mucosa by the inclusion of the short-chain fatty acids, yielding an improved overall treatment of these patients. In fact, because of the problems associated with calorie intake in bowel resection or other patients with intestinal problems, the structured lipid of the invention provides a more improved treatment than has otherwise previously been available.

**[0021]** The structured lipid of the invention may be used as part of a total parenteral nutrition diet or as a supplement to other diets. As part of a total parenteral nutrition diet, 2-5% linoleic acid is necessary as are standard essential amino acids and minerals common in all lipid-based nutritional diets. If used merely as a supplement rather than the basic calorie source of a diet, the structured lipid of the invention will assist in upkeep of the intestinal mucosa without deleterious effects.

**[0022]** The structured lipid of the invention may be manufactured by any conventional means such as transesterification but the use of blocking groups which allow positioning of the residues at specific locations is preferred. Those skilled in the art are familiar with the variety of techniques useful for directing the residues to particular locations and they need not be set forth here in detail. As noted, the two position appears to be most important in directing the triglyceride to the proper pathway intake and ease of breakdown.

## Claims

**Claims for the following Contracting Stat s : AT, BE, CH/LI, DE, DK, FR, GB, IT, LU, NL, SE**



1. A synthetic triglyceride of the form where $R_1$, $R_2$ and $R_3$ meet the following criteria:

   A. $R_1$, $R_2$ and $R_3$ are fatty acids with at least one, but not all, of $R_1$, $R_2$ and $R_3$ being a short-chain $C_2$-$C_5$ fatty acid

   B. the fatty acids constitute one short-chain fatty acid, one long-chain fatty acid, and one medium-chain fatty acid.

   C. $R_2$ is a medium-chain or short chain fatty acid.

2. The synthetic triglyceride of claim 1, wherein at least one of said long-chain fatty acids comprises an ω3 fatty acid having 18-22 carbon atoms in the carbon backbone; or wherein at least one of said long-chain fatty acids comprises an ω9 fatty acid.

3. A total parenteral nutrition diet for use in therapy and the diet having as its primary lipid source structured lipids in the form of triglycerides according to any one of the preceding claims.

4. A total parenteral nutrition diet for use in treating patients with difficulty obtaining feeding through the intestinal mucosa (e.g. patients who have had a small bowel resection), and the diet having as its primary lipid source structured lipids in the form of triglycerides according to claims 1 or 2.

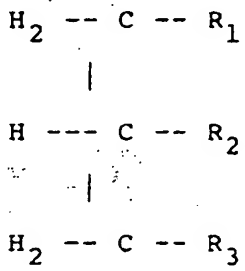
5. A parenteral diet for use in treating hypercatabolic patients and having as its primary lipid source structured lipids in the form of triglycerides according to claims 1 or 2.

6. Use of a synthetic triglyceride according to claims 1 or 2, for the manufacture of a total parenteral nutrition diet for treating patients having difficulty obtaining feeding through the intestinal mucosa, for example patients wh have had a small bowel resection.

7. Use of a synthetic triglyceride according to claims 1 or 2, for the manufacture of a parental diet for treating hypercatabolic patients.

**Claims for the following Contracting State : ES**

1. A method of manufacturing, by transesterification or the use of blocking groups, a synthetic triglyceride of the form



   where $R_1$, $R_2$ and $R_3$ meet the following criteria:

   A. $R_1$, $R_2$ and $R_3$ are fatty acids with at least one but not all, of $R_1$, $R_2$ and $R_3$ being a short chain $C_2$-$C_5$ fatty acid;
   B. the fatty acids constitute one short-chain fatty acid, one long-chain fatty acid and one medium-chain fatty acid;
   C. $R_2$ is a medium-chain or short-chain fatty acid.

2. The method of claim 1, wherein at least one of said long-chain fatty acids comprises an ω3 fatty acid having 18-22 carbon atoms in the carbon backbone; or wherein at least one of said long-chain fatty acids comprises an ω9 fatty acid.

3. A method according to claims 1 or 2, wherein the synthetic triglycerides form part of a total parenteral nutrition diet for use in therapy and the diet having as its primary lipid source structured lipids in the form of triglycerides as defined in any one of the preceding claims.

4. A method according to claims 1 or 2, wherein the synthetic triglycerides form part of a total parenteral nutrition diet for use in treating patients with difficulty obtaining feeding through the intestinal mucosa (e.g. patients who have had a small bowel resection), and the diet having as its primary lipid source structured lipids in the form of triglycerides as defined in any one of claims 1 to 2.

5. A method according to claims 1 or 2, wherein the synthetic triglycerides form part of a par nteral diet

for use in treating hypercatabolic patients and having as its primary lipid source structured lipids in the form of triglycerides as defined in claims 1 or 2.

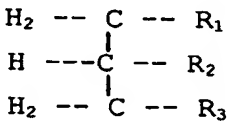
6. Use of a synthetic triglyceride according to claims 1 or 2, for the manufacture of a total parenteral nutrition diet for treating patients having difficulty obtaining feeding through the intestinal mucosa, for example patients who have had a small bowel resection.

7. Use of a synthetic triglyceride according to claims 1 or 2, for the manufacture of a parenteral diet for treating hypercatabolic patients.

**Patentansprüche**

**Patentansprüche für folgende Vertragsstaaten : AT, BE, CH/LI, DE, DK, FR, GB, IT, LU, NL, SE**

1. Synthetisches Triglycerid der Form



worin $R_1$, $R_2$ und $R_3$ folgende Kriterien erfüllen:

A. $R_1$, $R_2$ und $R_3$ Fettsäuren sind, wobei mindestens einer der Reste $R_1$, $R_2$ und $R_3$, jedoch nicht alle, eine kurzkettige C2 - C5-Fettsäure ist,
B. die Fettsäuren eine kurzkettige Fettsäure, eine langkettige Fettsäure und eine Fettsäure mit mittlerer Kettenlänge darstellen, und
C. $R_2$ eine Fettsäure mit mittlerer oder kurzer Kettenlänge ist.

2. Synthetisches Triglycerid gemäß Anspruch 1, worin mindestens eine der langkettigen Fettsäuren eine ω3-Fettsäure mit 18 - 22 Kohlenstoffatomen im Kohlenstoffgerüst oder mindestens eine der langkettigen Fettsäuren eine ω9-Fettsäure umfaßt.

3. Parenterale Komplettdiät zur therapeutischen Anwendung mit strukturierten Lipiden in Form von Triglyceriden gemäß einem der vorhergehenden Ansprüche als primäre Lipidquelle.

4. Parenterale Komplettdiät zur Behandlung von Patienten, die Schwierigkeiten bei der Ernährung über die Darmschleimhaut haben, (z. B. Patienten nach Dünndarm-Resektion) mit strukturierten Lipiden in Form von Triglyceriden gemäß Ansprüchen 1 oder 2 als primäre Lipidquelle.

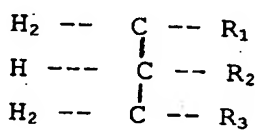
5. Parenterale Diät zur Behandlung v n hyperkatabolischen Patienten mit strukturierten Lipiden in Form von Triglyceriden gemäß Ansprüchen 1 oder 2 als primäre Lipidquelle.

6. Verwendung eines synthetischen Triglycerids gemäß Ansprüchen 1 oder 2 zur Herstellung einer parenteralen Komplettdiät zur Behandlung von Patienten, die Schwierigkeiten bei der Ernährung über die Darmschleimhaut haben, z. B. Patienten nach Dünndarm-Resektion.

7. Verwendung eines synthetischen Triglycerids gemäß Ansprüchen 1 oder 2 zur Herstellung einer parenteralen Diät zur Behandlung von hyperkatabolischen Patienten.

**Patentansprüche für folgenden Vertragsstaat : ES**

1. Verfahren zur Herstellung eines synthetischen Triglycerids der Form



durch Umesterung oder Verwendung von Schutzgruppen, worin $R_1$, $R_2$ und $R_3$ folgende Kriterien erfüllen:

A. $R_1$, $R_2$ und $R_3$ Fettsäuren sind, wobei mindestens einer der Reste $R_1$, $R_2$ und $R_3$, jedoch nicht alle, eine kurzkettige $C_2$-$C_5$-Fettsäure ist,
B. die Fettsäuren eine kurzkettige Fettsäure, eine langkettige Fettsäure und eine Fettsäure mit mittlerer Kettenlänge darstellen, und
C. $R_2$ eine Fettsäure mit mittlerer oder kurzer Kettenlänge ist.

2. Verfahren gemäß Anspruch 1, worin mindestens eine der langkettigen Fettsäuren eine ω3-Fettsäure mit 18 - 22 Kohlenstoffatomen im Kohlenstoffgerüst oder mindestens eine der langkettigen Fettsäuren eine ω9-Fettsäure umfaßt.

3. Verfahren gemäß Ansprüchen 1 oder 2, worin die synthetischen Triglyceride Bestandteil einer parenteralen Komplettdiät zur therapeutischen Anwendung sind und die Diät als primäre Lipidquelle strukturierte Lipide in der Form von Triglyceriden gemäß einem der vorhergehenden Ansprüche enthält.

4. Verfahren gemäß Ansprüchen 1 oder 2, worin die synthetischen Triglyceride Bestandteil einer parenteralen Komplettdiät sind zur Behandlung von Patienten, die Schwierigkeiten bei der Ernährung über die Darmschleimhaut haben, (z. B. Patienten nach Dünndarm-Resektion) und die Diät als primäre Lipidquelle strukturierte Lipide in Form von Triglyceriden gemäß Ansprüchen 1 oder 2 enthält.

5. Verfahren gemäß Ansprüchen 1 oder 2, worin die synthetischen Triglyceride Bestandteil einer parenteralen Diät zur Behandlung von hyperkatabolischen Patienten ist und als primäre Lipidquelle strukturierte Lipide in Form von Triglyceriden gemäß Ansprüchen 1 oder 2 enthalten.

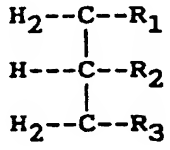
6. Verwendung eines synthetischen Triglycerids gemäß Ansprüchen 1 oder 2 zur Herstellung einer parenteralen Komplettdiät zur Behandlung von Patienten, die Schwierigkeiten bei der Ernährung über die Darmschleimhaut haben, z. B. Patienten nach Dünndarm-Resektion.

7. Verwendung eines synthetischen Triglycerids gemäß Ansprüchen 1 oder 2 zur Herstellung einer parenteralen Diät zur Behandlung von hyperkatabolischen Patienten.

**Revendications**

**Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE**

1. Un triglycéride synthétique de la forme



dans lequel $R_1$, $R_2$ et $R_3$ satisfont les critères suivants:

A. $R_1$, $R_2$ et $R_3$ sont des acides gras, l'un au moins, mais pas tous, parmi $R_1$, $R_2$ et $R_3$, étant un acide gros à chaîne courte $C_2$-$C_5$;
B. lesdits acides gras constituent un acide gras à chaîne courte, un acide gras à longue chaîne et un acide gras à chaîne moyenne,
C. $R_2$ est un acide gras à chaîne moyenne ou un acide gras à chaîne courte.

2. Le triglycéride synthétique de la revendication 1, dans lequel au moins un desdits acides gras à longue chaîne comprend un acide gras ω3 ayant 18-22 atomes de carbone dans le squelette carboné; ou dans lequel au moins un desdits acides gras à longue chaîne comprend un acide gras ω9.

3. Un régime nutritionnel parentéral total, pour une utilisation en thérapie, le régime ayant comme source lipidique principale des lipides structurés de la forme des triglycérides, selon l'une quelconque des revendications précédentes.

4. Un régime nutritionnel parentéral total, pour une utilisation dans le traitement de patients ayant une obtention difficile de nourriture à travers la muqueuse intestinale (p.ex. des patients qui ont eu une petite résection intestinale), le régime ayant comme source lipidique principale des lipides structurés de la forme des triglycérides, selon les revendications 1 ou 2.

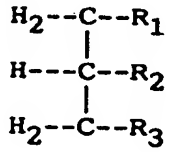
5. Un régime parentéral, pour une utilisation dans le traitement de patients hypercataboliques et ayant comme source lipidique principale des lipides structurés de la forme des triglycérides, selon les revendications 1 ou 2.

6. Utilisation d'un triglycéride synthétique, selon les revendications 1 ou 2 pour l'élaboration d'un régime nutritionnel parentéral total pour traiter des patients ayant une obtention difficile de nourriture à travers la muqueuse intestinale, par exemple des patients qui ont eu une petite résection intestinale.

7. Utilisation d'un triglycéride synthétique, selon les revendications 1 ou 2 pour l'élaboration d'un régime parentéral, pour le traitement de patients hypercataboliques.

**Revendications pour l'Etat contractant suivant : ES**

1. Une méthode de fabrication, par transestérification ou par l'utilisation de groupes bloquants, d'un triglycéride synthétique de la forme



dans lequel $R_1$, $R_2$ et $R_3$ satisfont les critères suivants:

A. $R_1$, $R_2$ et $R_3$ sont des acides gras, l'un au moins, mais pas tous, parmi $R_1$, $R_2$ et $R_3$, étant un acide gras à chaîne courte $C_2$-$C_5$;

B. lesdits acides gras constituent un acide gras à chaîne courte, un acide gras à longue chaîne et un acide gras à chaîne moyenne;

C. $R_2$ est un acide gras à chaîne moyenne ou un acide gras à chaîne courte.

2. La méthode de la revendication 1, dans laquelle au moins un desdits acides gras à longue chaîne comprend un acide gras ω3 ayant 18-22 atomes de carbone dans le squelette carboné; ou dans laquelle au moins un desdits acides gras à longue chaîne comprend un acide gras ω9.

3. Une méthode, selon les revendications 1 ou 2, dans laquelle les triglycérides synthétiques forment une partie d'un régime nutritionnel parentéral total, pour une utilisation en thérapie, le régime ayant comme source lipidique principale des lipides structurés de la forme des triglycérides tels que définis dans l'une quelconque des revendications précédentes.

4. Une méthode, selon les revendications 1 ou 2, dans laquelle les triglycérides synthétiques forment une partie d'un régime nutritionnel parentéral total, pour une utilisation dans le traitement de patients ayant une obtention difficile de nourriture à travers la muqueuse intestinale (p.ex. des patients qui ont eu une petite résection intestinale), le régime ayant comme source lipidique principale des lipides structurés de la forme des triglycérides tels que définis dans les revendications 1 ou 2.

5. Une méthode, selon les revendications 1 ou 2, dans laquelle les triglycérides synthétiques forment une partie d'un régime parentéral, pour une utilisation dans le traitement de patients hypercataboliques et ayant code source lipidique principale des lipides structurés de la forme des triglycérides tels que définis dans les revendications 1 ou 2.

6. Utilisation d'un triglycéride synthétique selon les revendications 1 ou 2, pour l'élaboration d'un régime nutritionnel parentéral total pour traiter des patients ayant une obtention difficile de nourriture à travers la muqueuse intestinale, par exemple des patients qui ont eu une petite résection intestinale.

7. Utilisation d'un triglycéride synthétique, selon les revendications 1 ou 2, pour l'élaboration d'un régime parentéral, pour le traitement de patients hypercataboliques.